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(54) **Leukotriene antagonists.**

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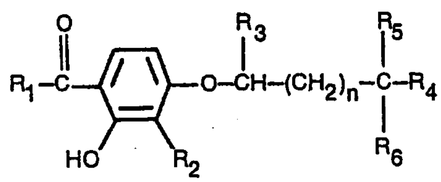
Description

Research in the area of allergic reactions of the lung has provided evidence that arachidonic acid derivatives formed by the action of lipoxygenases are related to various disease states. Some of these arachidonic acid metabolites have been classified as members of a family of eicosatetraenoic acids termed leukotrienes. Three of these substances are currently thought to be major components of what has been previously called slow reacting substance of anaphylaxis (SRS—A).

European Patent Application No. 28063 is directed to a series of phenoxyalkoxyphenyl derivatives which are reported to be antagonists of SRS—A and DE 2 250 327 discloses some compounds of similar structure with pharmacological properties.

This invention provides chemical agents which are potent, selective leukotriene antagonists that can be used therapeutically in the treatment of allergic disorders such as asthma, where leukotrienes are thought to be causal mediators. Certain of the compounds are disclosed as intermediates in British patents 1 524 260 and 2 118 184.

More specifically this invention provides compounds of the Formula I



I

and pharmaceutically acceptable salts thereof, for use as pharmaceuticals, wherein:

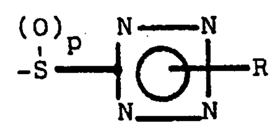
R_1 is hydrogen, C_1—C_8 alkyl or C_3—C_8 cycloalkyl;

R_2 is hydrogen, C_1—C_6 alkyl, or C_2—C_6 alkenyl;

R_3 is hydrogen, C_1—C_{10} alkyl, phenyl, C_1—C_{10} alkyl-substituted phenyl, biphenyl, or benzylphenyl;

R_4 is —$COOR_7$, —$CONR_8R_9$, —CONHOH, —SC(=NH)NH_2, cyano, thiocyanato,

or



where R_7 is hydrogen or C_1—C_4 alkyl,

R_8 and R_9 are each independently hydrogen, C_1—C_3 alkyl, or when taken together with the nitrogen atom form a morpholine or N-methyl piperazine ring,

R is hydrogen, C_1—C_4 alkyl, or —CH_2COOR_7, and

p is 0, 1, or 2;

R_5 and R_6 are each independently hydrogen or C_1—C_3 alkyl; and

n is 0—10.

Compounds of formula (I) are novel, provided that (a) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is —$COOCH_3$, n is 0 to 2 or 4—10, and (b) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is —$COOC_2H_5$, n is 0 or 2—10.

Compounds of formula (I) wherein R^4 is cyano or thiocyanato are useful as intermediates in the preparation of certain of the other compounds of this invention. The remaining compounds of formula (I) are useful in treatment of immediate hypersensitivity conditions such as asthma.

A preferred group of compounds are the compounds of Formula I wherein:

(a) R_1 is C_1—C_6 alkyl, especially methyl,

(b) R_2 is C_1—C_6 alkyl, especially propyl,

(c) R_2 is C_3—C_6 alkenyl, especially allyl,

(d) R_3 is hydrogen,

(e) R_5 is hydrogen,

(f) R_6 is hydrogen,

(g) R_4 is —COOH,

(h) R_4 is 5-tetrazolyl (R is hydrogen),

(i) R_4 is 5-tetrazolylthio (R is hydrogen and p is 0), and

(j) n is 1—4, especially where n is 1 or 2.

Especially preferred compounds of Formula I are those wherein R_1 is methyl and R_2 is propyl. Also especially preferred are those compounds wherein R_4 is 5-tetrazolyl (R is hydrogen), 5-tetrazolylthio (R is hydrogen and p is 0), or —COOH.

The following definitions refer to the various terms used throughout this disclosure.

The term "C_1—C_{10} alkyl" refers to the straight and branched aliphatic radicals of 1 to 10 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, sec-isoamyl (1,2-dimethylpropyl), tert-amyl (1,1-dimethylpropyl), hexyl, isohexyl (4-methylpentyl), sec-hexyl (1-methylpentyl), 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, isoheptyl (5-methylhexyl), sec-heptyl (1-methylhexyl), 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, isooctyl (6-methylheptyl), sec-octyl (1-methylheptyl), tert-octyl (1,1,3,3-tetramethylbutyl), nonyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-methyloctyl, 1-, 2-, 3-, 4-, or 5-ethylheptyl, 1-, 2-, or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-methoxynonyl, 1-, 2-, 3-, 4-, 5-, or 6-ethyloctyl and 1-, 2-, 3-, or 4-propylheptyl. The term "C_1—C_{10} alkyl" includes within its definition the terms "C_1—C_3 alkyl", "C_1—C_4 alkyl", and "C_1—C_6 alkyl".

The term "C_3—C_8 cycloalkyl" refers to the saturated alicyclic rings of three to eight carbon atoms such as cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl.

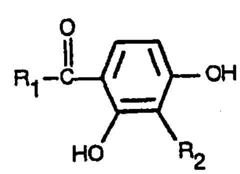
The term "C_2—C_6 alkenyl" refers to straight and branched radicals of two to six carbon atoms such as ethenyl, allyl, isopropenyl, butenyl, isobutenyl, 3-methyl-2-butenyl and n-hexenyl, and includes the term "C_3—C_6 alkenyl".

The pharmaceutically acceptable base addition salts of this invention include salts derived from inorganic bases, such as ammonium and alkali and alkaline earth metal hydroxides, carbonates and bicarbonates, as well as salts derived from non-toxic basic organic amines, such as aliphatic and aromatic amines, aliphatic diamines and hydroxyalkylamines. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methyl amine, diethyl amine, ethylene diamine, cyclohexylamine and ethanolamine. The potassium and sodium salt forms are particularly preferred.

In addition, when the compounds of formula I are amine derivatives (*e.g.* R_4 is —SC(=NH)NH_2), the compounds may also exist as the corresponding acid addition salts. The pharmaceutically acceptable acid addition salts of this invention therefore also include salts derived from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid and phosphorous acid, as well as salts derived from nontoxic organic acids such as aliphatic mono and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic and alkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, benzenesulfonate, toluenesulfonate, chlorobenzenesulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, malate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate and naphthalene-2-sulfonate. Salts from inorganic acids are preferred, especially the hydrochloride or hydrobromide salts.

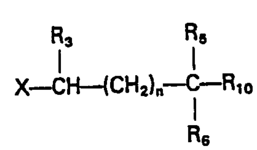
It is recognized that if R_3 is other than hydrogen and/or if R_5 is different from R_6, various stereoisomers will exist. This invention is not limited to any particular stereoisomer but includes all possible individual isomers and racemates of the compounds of Formula I.

The compounds of this invention may be prepared by the reaction of a phenol of the formula



II

wherein R_1 and R_2 are described hereinabove, with a compound of the formula



III

wherein R_3, R_5, R_6, and n are as described herinabove, X is a suitable leaving group, such as halo or a sulfonic ester group, and R_{10} is a protected acid ester, such as —COO(C_1—C_4 alkyl) or a benzhydryl ester, or is cyano or thiocyanato. The reaction between compounds II and III is usually performed in equimolar amounts although ratios other than equimolar amounts are completely operative. The reaction is best

carried out in a nonreactive solvent such as ketones, especially acetone or methyl ethyl ketone, and in the presence of a base, preferably an alkali metal hydroxide or carbonate, preferably potassium carbonate. Especially when X is chloro, a catalyst such as potassium or sodium iodide may be added to increase the reaction rate. The reaction may be carried out at temperatures of about ambient temperature up to the boiling point of the reaction mixture, the latter being preferred.

In the case where R_{10} is cyano, the resulting derivative of Formula I may be converted to the compounds of this invention by the following methods. Compounds of Formula I wherein R_4 is —COOH may be obtained by hydrolysis of the intermediate cyano derivative. This is generally accomplished by heating the cyano derivative in aqueous alcohols in the presence of a base such as sodium hydroxide. Alternatively, the carboxylic acid derivatives (I, R_4 is —COOH) may be prepared by the hydrolysis of the corresponding ester derivatives. This may be accomplished by an aqueous hydrolysis as described above or, especially in the case of a diphenylmethyl (benzhydryl) ester, using such methods known in the art such as treating with formic acid and triethylsilane followed by an aqueous workup, acidic hydrolysis, treatment with trifluoroacetic acid in anisole, or catalytic hydrogenation. The required benzhydryl ester starting materials (III, R_{10} is a benzhydryl ester) may be prepared from the corresponding carboxylic acids (III, R_{10} is —COOH) in the usual ways, such as treatment with diphenyldiazomethane in methylene chloride or heating with benzhydrol and a mineral acid in a solvent such as toluene with the azeotropic removal of water.

Alternatively, the compounds of Formula I wherein R_4 is —$COOR_7$ and R_7 is C_1—C_4 alkyl may be prepared by conventional methods of esterification from the respective acid derivatives or are prepared directly by the methods described below.

Salts may be prepared by treating the corresponding acids (R_4 is —COOH) with an appropriate base in the normal manner.

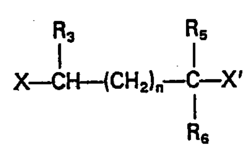
Amide derivatives (R_4 is —$CONR_8R_9$ or —CONHOH) may be prepared by direct aminolysis of the corresponding ester, or from the corresponding carboxylic acid using conventional means such as conversion to the acid chloride followed by reaction of the acid chloride with an appropriate amine or treatment with an agent such as 1,1′-carbonyldiimidazole in the presence of an appropriate amine. In either case, the ester or acid is reacted with the appropriate amine VI

$$HNR_8R_9 \qquad \text{VI}$$

wherein R_8 and R_9 are as described hereinabove, or hydroxylamine, the latter giving the hydroxamic acid derivative.

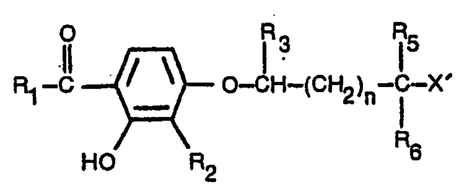
The compounds of Formula I wherein R_4 is 5-tetrazolyl (R is hydrogen) are prepared by treating the cyano intermediate with an alkali metal azide such as sodium azide, ammonium chloride, and (optionally) lithium chloride in a non-reactive high-boiling solvent such as N,N-dimethylformamide, preferably at temperatures from 60°C to the reflux temperature of the reaction mixture. The thiotetrazole compounds of Formula I are prepared from the thiocyanato intermediates in a similar manner.

Alternatively the compounds of Formula I may be prepared by the reaction of the phenol of Formula II with a compound of the Formula IV



IV

wherein R_3, R_5, R_6, and n are the same as described hereinabove and X and X′ are the same or different leaving groups, such as halo or sulfonic ester groups. The resulting products are those having the formula



V

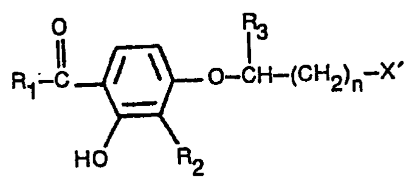
wherein R_1, R_2, R_3, R_5, R_6, n, and X′ are the same as described hereinabove. As those skilled in the art will recognize, when the substituents R_3, R_5, and R_6 afford a symmetrically-substituted dihaloalkane IV, X and X′ may be the same or different leaving groups since the reaction with phenol II will give the same product V regardless which "end" of the molecule reacts. However, when alkane IV is non-symmetrically substituted, those skilled in the art will recognize that X should be a better leaving group than X′ in order for the desired product V to be formed. If X′ is the better leaving group in compound IV, IV can first be converted to a

compound such as III (e.g., reaction of IV with an alkali metal cyanide to give III where R_{10} is —CN) which can then be reacted with phenol II as previously described.

The compounds of Formula V may be transformed into the compounds of this invention in the following manner. When compounds of Formula V are heated with an alkali metal cyanide, such as sodium cyanide, in the presence of a high boiling, nonreactive solvent, such as N,N-dimethylformamide, at elevated temperatures (50°C to the reflux temperature of the solvent), the intermediate cyano compound of Formula I' is produced which may then be transformed into the acid, ester, or tetrazole derivatives as described previously. Similarly, the thiotetrazole compounds of this invention can be prepared by reacting a compound of Formula V with an alkali metal thiocyanate in a similar manner to give the intermediate thiocyanato compound of Formula I', followed by transformation to the thiotetrazole in the usual manner.

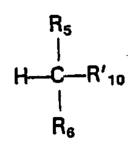
The isothiourea and thiotetrazole compounds may be prepared from intermediate V by recting with thiourea and 5-mercaptotetrazole, respectively. In either case, the reaction is performed by stirring the two reactants in a non-reactive solvent preferably at room to reflux temperature for about two to three days. In the thiourea reaction, ethanol is the preferred solvent and the product is usually isolated as the isothiuronium hydrohalide salt which is formed directly. In the 5-mercaptotetrazole reaction, the preferred solvent is dimethylformamide and an acid scavenger, such as an alkali metal-carbonate, is preferably included in the reaction.

Especially in the instances where R_5 and/or R_6 are other than hydrogen, compounds of Formula I may be prepared by the reaction of a compound of Formula V'



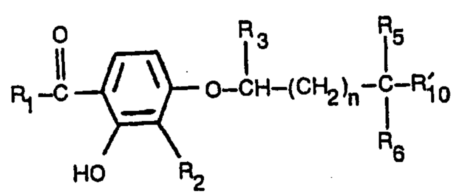
V'

with an alkane of the formula VII



VII

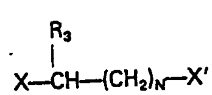
wherein R_1, R_2, R_3, R_5, R_6, X', and n are the same as previously defined and R'_{10} is cyano (—CN) or a carboxylic ester, to give a compound of the Formula I''



I''

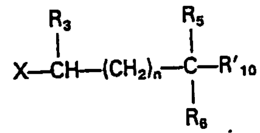
which can then be transformed into the compounds of this invention by the methods previously described. The reaction of compounds V' and VII is performed by first preparing the anion of compound VII by treating VII with a strong base, such as sodium metal dissolved in liquid ammonia with a catalytic amount of ferric chloride, sodium hydride or diisopropyl lithium amide in solvents such as tetrahydrofuran or dimethylformamide. The anion thus formed is treated with the intermediate V' (preferably where X' is bromo) which gives I''.

Alternatively, I'' may be prepared by first reacting the anion of VII with compound IV'



IV'

where n, R_3, X, and X' are the same as previously defined, and, where IV' is unsymmetrical, X' is a better leaving group than X, preferably bromo, to give intermediate III'



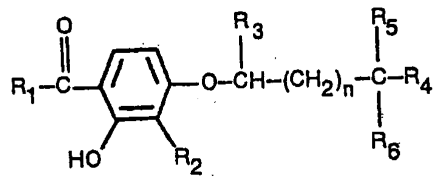
III'

which can then be condensed with phenol II and transformed in the usual manner.

The thiotetrazole derivatives of this invention (p is 0) may be transformed into the corresponding sulfoxide (p is 1) compounds upon treatment with a mild oxidizing agent, such as hydrogen peroxide in methanol or an alkali metal periodate in aqueous alcohol. The corresponding sulfones (p is 2) are prepared from the thio or sulfoxide compounds on treatment with a strong oxidizing agent such as hydrogen peroxide in acetic acid or m-chloroperbenzoic acid in methanol.

When R is hydrogen, the tetrazole and thiotetrazole moieties exist in equilibrium between the 1H and 2H tautomers. To provide compounds where R is other than hydrogen, the 5-tetrazole and 5-thiotetrazole compounds may be alkylated with the appropriate alkyl halide or alkyl haloacetate to give both the 1- and 2-substituted 5-tetrazole and 5-thiotetrazole compounds which may be separated by such methods as chromatography or crystallization. Compounds where R is $-CH_2COOH$ may be prepared from the corresponding esters by hydrolysis in the usual manner.

Accordingly, the invention also provides a process for preparing a compound of the formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

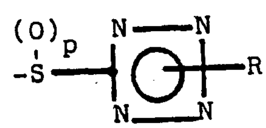
R_1 is hydrogen, C_1—C_8 alkyl or C_3—C_8 cycloalkyl;

R_2 is hydrogen, C_1—C_6 alkyl, or C_2—C_6 alkenyl;

R_3 is hydrogen, C_1—C_{10} alkyl, phenyl, C_1—C_{10} alkyl-substituted phenyl, biphenyl, or benzylphenyl;

R_4 is $-COOR_7$, $-CONR_8R_9$, $-CONHOH$, $-SC(=NH)NH_2$, cyano, thiocyanato,

or



where R_7 is hydrogen or C_1—C_4 alkyl,

R_8 and R_9 are each independently hydrogen, C_1—C_3 alkyl, or when taken together with the nitrogen atom form a morpholine or N-methyl piperazine ring,

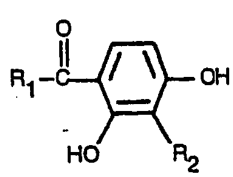
R is hydrogen, C_1—C_4 alkyl, or $-CH_2COOR_7$, and

p is 0, 1, or 2;

R_5 and R_6 are each independently hydrogen or C_1—C_3 alkyl; and

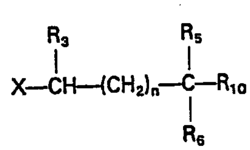
n is 0—10; provided that (a) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is $-COOCH_3$, n is 0 to 2 or 4—10, and (b) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is $-COOC_2H_5$, n is 0 or 2—10; which comprises

a) reacting a compound of formula (II)



II

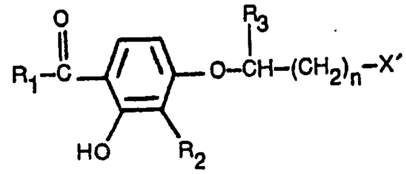
wherein R_1 and R_2 are as defined in claim 1, with a compound of formula (III)



(III)

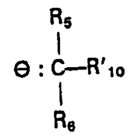
where R_3, R_5, R_6 and n are as defined in formula (I), X is a leaving group, and R_{10} is cyano, thiocyanato, or —$COOR_7$, where R_7 is as defined in formula (I), to provide a compound of formula (I) wherein R_4 is cyano, thiocyanato or —$COOR_7$; or

b) reacting a compound of formula



V'

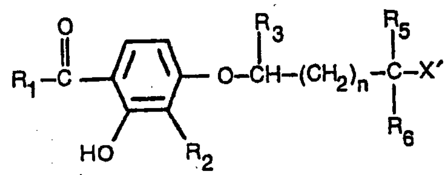
where R_1, R_2, R_3, and n are as defined in formula (I) and X' is a leaving group, with a source of a carbanion of the formula



(VII')

where R_5 and R_6 are as defined in formula (I) and R'_{10} is cyano or $COOR_7$, where R_7 is C_1—C_4 alkyl, to provide a compound of formula (I) wherein R_4 is cyano or $COOR_7$; or

c) reacting a compound of formula (V)



V

where R_1, R_2, R_3, R_5 and R_6 are as defined in formula (I) and X' is a leaving group, with

1) an alkali metal cyanide to provide a compound of formula (I) wherein R_4 is cyano, or

2) an alkali metal thiocyanate to provide a compound of formula (I) wherein R_4 is thiocyanato, or

4) thiourea to provide a compound of formula (I) wherein R_4 is —$SC(=NH)NH_2$, or

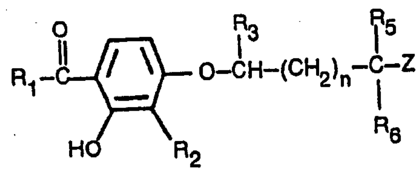
5) 5-mercaptotetrazole to provide a compound of formula (I) wherein R_4 is tetrazolylthio; or

d) hydrolyzing a compound of formula (I) wherein R_4 is cyano to provide a compound of formula (I) wherein R_4 is carboxyl, or

e) reacting a compound of formula (I) wherein R_4 is cyano with an alkali metal azide and ammonium-chloride to provide a compound of formula (I) wherein R_4 is 5-tetrazolyl; or

f) reacting a compound of formula (I) wherein R_4 is thiocyanato with an alkali metal azide and ammonium-chloride to provide a compound of formula I wherein R_4 is tetrazolylthio,

g) reacting a compound of formula (VIII)



(VIII)

wherein R_1, R_2, R_3, R_5, R_6 and n are as defined in formula (I) and Z is a protected acid ester or —COCl

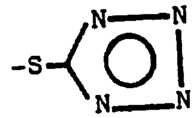
1) with water to provide a compound of formula (I) wherein R_4 is carboxyl, or

2) with HNR_8R_9, where R_8 and R_9 are as defined in formula (I) to provide a compound of formula (I) wherein R_4 is $CONR_8R_9$, or

3) with H_2NOH to provide a compound of formula (I) wherein R_4 is —CONHOH; or

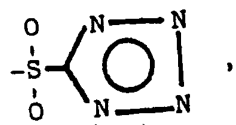
h) esterifying a compound of formula (I) wherein R_4 is carboxyl to provide a compound of formula (I) wherein R_4 is $COOR_7'$ where R_7' is C_1—C_4 alkyl, or

i) reacting a compound of formula (I) wherein R_4 is

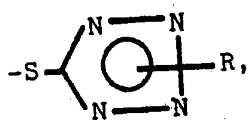


1) with a mild oxidizing agent to produce a compound of formula (I) wherein R_4 is

2) with a strong oxidizing agent to provide a compound of formula (I) wherein R_4 is

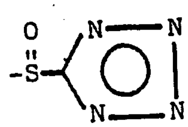


3) with an alkyl halide or alkyl haloacetate to provide a compound of formula wherein R_4 is

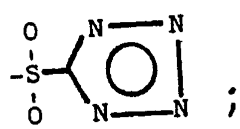


when R is as defined in formula (I); or

j) reacting a compound of formula I wherein R_4 is

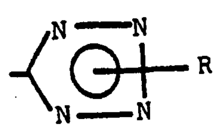


with a strong oxidizing agent to provide a compound of formula (I) wherein R_4 is



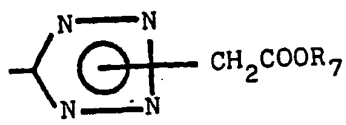
k) reacting a compound of formula (I) wherein R_4 is

with an alkyl halide or an alkyl halo acetate to provide a compound of formula (I) wherein R_4 is



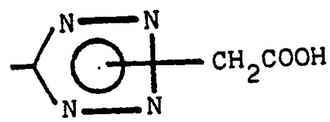
where R is C_1—C_4 alkyl or —CH_2COOR_7 where R_7 is C_1—C_4 alkyl; or

l) hydrolyzing a compound of formula I wherein R_4 is

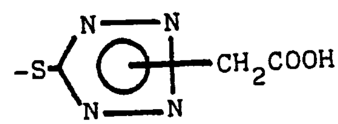


or

where R_7 is C_1—C_4 alkyl, to provide a compound of formula I wherein R_4 is



or



;

m) salifying a compound of formula (I).

Intermediate compounds II, III, IV, IV', VI and VII are either commercially available, known in the literature, or can be prepared according to methods known in the art.

The following preparations and examples further illustrate the preparation of the starting materials, intermediates, and compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention. The term "m/e" used in characterizing the products refers to the mass-to-charge ratio of ions which appear in the mass spectra of the products. In general, the values correspond to molecular weights of the major peaks, and are so designated "M^+". Where structures were confirmed by infra-red or proton nuclear magnetic resonance analysis, the compound is so designated by "IR" and/or "NMR", respectively.

Example 1

5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentane nitrile

A. Preparation of 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl bromide.

A solution of 50 g. (257 mmoles) of 2,4-dihydroxy-3-propylacetophenone in 300 ml. of acetone was slowly dripped into a refluxing solution of 221.98 g. (1.028 moles) of 1,4-dibromobutane, 35.52 g. (257 mmoles) of potassium carbonate, and 4.5 g. of potassium iodide in 800 ml. of acetone over a period of 3 hours. The solution was allowed to reflux for about 19 hours. The solution was filtered warm and the filtrate was evaporated *in vacuo*. Distillation of the resulting yellow oil at 0.25 mm. of Hg resulted in the recovery of the excess dibromobutane (at about 30°C) and 66.12 grams of the desired 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl bromide at 180°C.

B. Preparation 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentane nitrile.

A solution of 30.0 g. (91.1 mmoles) of 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl bromide and 4.91 g. (100.2 mmoles) of sodium cyanide in 225 ml. of dimethylformamide was heated to 75—85°C for about 17 hours. The reaction mixture was cooled to room temperature, filtered, and evaporated *in vacuo* at 75°C. Cold 0.1N hydrochloric acid was added to the residue, and the residue was extracted into ethyl acetate. The ethyl acetate layer was twice washed with 0.1N hydrochloric acid, dried over sodium sulfate, and evaporated *in vacuo* to yield 21.02 g. of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentane nitrile as a dark amber oil which crystallized as it cooled.

Analysis: $C_{16}H_{21}NO_3$:

Calc.: C, 69.79; H, 7.69; N, 5.09;
Found: C, 69.49; H, 7.42; N, 5.20.

Examples 2—7

The following nitrile intermediates were prepared according to the procedure in Example 1 using the appropriate dibromoalkane. The compounds were all oils which were used in subsequent transformations without further purification. Yields are expressed as the percent molar yield from the bromide intermediate.

2. 7-(4-Acetyl-3-hydroxy-2-propylphenoxy)heptane nitrile, 98% yield.

Analysis: $C_{18}H_{25}NO_3$;
Calc.: C, 71.26; H, 8.31; N, 4.62;
Found: C, 71.03; H, 8.04; N, 4.69.

3. 8-(4-Acetyl-3-hydroxy-2-propylphenoxy)octane nitrile, 83% yield.

Analysis: $C_{19}H_{27}NO_3$;
Calc.: C, 71.89; H, 8.57; N, 4.41;
Found: C, 72.16; H, 8.71; N, 4.69.

4. 9-(4-Acetyl-3-hydroxy-2-propylphenoxy)nonane nitrile, 86% yield.
Analysis: $C_{20}H_{29}NO_3$;
Calc.: C, 72.47; H, 8.82; N, 4.23;
Found: C, 70.97; H, 8.89; N, 4.21.

5. 10-(4-Acetyl-3-hydroxy-2-propylphenoxy)-decane nitrile, ca. 100% yield.
Analysis: $C_{21}H_{31}NO_3$;
Cal.: C, 73.01; H, 9.04; N, 4.05;
Found: C, 72.75; H, 8.99; N, 4.01.

6. 11-(4-Acetyl-3-hydroxy-2-propylphenoxy)-undecane nitrile, ca. 100% yield.
Analysis: $C_{22}H_{33}NO_3$;
Calc.: C, 73.50; H, 9.25; N, 3.90;
Found: C, 64.48; H, 9.19; N, 2.97.

7. 13-(4-Acetyl-3-hydroxy-2-propylphenoxy)-tridecane nitrile, 95% yield.
Analysis: $C_{24}H_{37}NO_3$;
Calc. C, 74.38; H, 9.62; N, 3.61;
Found: C, 74.16; H, 9.41; N, 3.41.

Example 8

5-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)-butyl]-tetrazole

A solution of 20.73 g. (75 mmoles) of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentane nitrile, 14.63 g. (225 mmoles) of sodium azide, and 12.04 g. (225 mmoles) of ammonium chloride in 200 ml. of dimethylformamide was heated at 125°C for about 17 hours. At this time an additional 9.75 g. (150 mmoles) of ammonium chloride were added and the heating was continued for an additional 6 hours. The reaction mixture was filtered hot and evaporated to dryness *in vacuo* yielding a viscous dark oil. The residue was treated with dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and evaporated *in vacuo* yielding an oil which crystallized upon cooling. The crystals were boiled with decolorizing carbon in ethyl acetate for about 30 minutes. The solution was filtered hot, and the filtrate was cooled in the refrigerator to yield orange-amber crystals. The crystals were collected by vacuum filtration and washed with ethyl acetate to give 6.49 g. of the title product, m.p. about 113.5—115°C.

Analysis: $C_{16}H_{22}N_4O_3$;
Calc.: C, 60.36; H, 6.97; N, 17.60; O, 15.08;
Found: C, 60.14; H, 6.86; N, 17.75; O, 15.12.

Examples 9—14

The following tetrazole compounds were prepared from the respective nitrile intermediates following the procedure of Example 8. Yields are expressed as the molar percent yield from the nitrile intermediate.

9. 5-[6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-hexyl]-tetrazole, m.p. about 86.5—90°C, 8% yield.
Analysis: $C_{18}H_{26}N_4O_3$;
Calc.: C, 62.41; H, 7.57; N, 16.17; O, 13.85;
Found: C, 62.17; H, 7.37; N, 16.41; O, 14.14.

10. 5-[7-(4-Acetyl-3-hydroxy-2-propylphenoxy)heptyl]-tetrazole, m.p. about 92-93.5°C, 35% yield.
Analysis: $C_{19}H_{28}N_4O_3$;
Calc.: C, 63.31; H, 7.83; N, 15.54;
Found: C, 63.54; H, 8.01; N, 15.70.

11. 5-[8-(4-Acetyl-3-hydroxy-2-propylphenoxy)octyl]-tetrazole, m.p. about 82.5—84.5°C, 4% yield.
Analysis: $C_{20}H_{30}N_4O_3$;
Calc.: C, 64.15; H, 8.08; N, 14.96; O, 12.82;
Found: C, 64.12; H, 7.82; N, 15.06; O, 12.99.

12. 5-[9-(4-Acetyl-3-hydroxy-2-propylphenoxy)nonyl]-tetrazole, m.p. about 107—115°C, 68% yield.
Analysis: $C_{21}H_{32}N_4O_3$;
Calc.: C, 64.92; H, 8.30; N, 14.42; O, 12.35;
Found: C, 64.66; H, 8.49; N, 14.15; O, 12.61.

13. 5-[10-(4-Acetyl-3-hydroxy-2-propylphenoxy)decyl]-tetrazole, m.p. about 74.5—84.5°C, 18% yield.
Analysis: $C_{22}H_{34}N_4O_3$;
Calc.: C, 65.64; H, 8.51; N, 13.92; O, 11.92;
Found: C, 65.59; H, 8.47; N, 14.11; O, 11.67.

14. 5-[12-(4-Acetyl-3-hydroxy-2-propylphenoxy)dodecyl]-tetrazole, m.p. about 84—88°C, 51% yield.
Analysis: $C_{24}H_{38}N_4O_3$;
Calc.: C, 66.95; H, 8.90; N, 13.01;
Found: C, 67.13; H, 8.77; N, 13.13.

Example 15

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-6-(4-benzylphenyl)hexanoic acid

A. Preparation of adipic acid monomethylester monoacid chloride.

One hundred grams of adipic acid monomethylester and 200 ml. of thionyl chloride were added to 300

ml. of methylene chloride followed by the addition of 1 ml. of dimethylformamide. The reaction was stirred at reflux for about 16 hours. After cooling, the reaction mixture was evaporated *in vacuo*. The resulting orange oil was vacuum distilled at 5 mm. of Hg. The distillate was collected from 97—100°C with most of the distillate coming at 98.5°C. A total of 95.7 g. of a light orange oil were collected and identified as adipic acid monomethyl ester monoacid chloride by NMR.

B. Preparation of methyl 6-(4-benzylphenyl)-6-oxo-hexanoate.

A solution of 45.8 g. of adipic acid monomethylester monoacid chloride and 40.0 g. of diphenylmethane in 1000 ml. of methylene chloride was cooled to about −10°C using an external ice/ethanol bath. Aluminum chloride (66.5 g.) was added over a two hour period keeping the temperature between −8 and −10°C. The reaction mixture was then added to a slush of hydrochloric acid in ice (total volume of 4000 ml.). The methylene chloride layer was separated and evaporated *in vacuo* leaving a light peach-colored viscous liquid which began to crystallize as it cooled. The material was vacuum distilled at 0.5 mm. of Hg from about 190 to 235°C giving 34.7 g. of methyl 6-(4-benzylphenyl)-6-oxo-hexanoate.

C. Preparation of ethyl 6-(4-benzylphenyl)-6-hydroxy-hexanoate.

A solution of 34.7 g. of methyl 6-(4-benzylphenyl)-6-oxo-hexanoate in 300 ml. of ethanol was treated with 5.1 g. of sodium borohydride and the reaction mixture stirred for about 17 hours. The ethanol was removed by evaporating *in vacuo*. The residue was treated with cold dilute hydrochloric acid and was then extracted twice with ethyl acetate. The combined ethyl acetate layers were washed with water, dried over sodium sulfate, and evaporated *in vacuo* giving 26.6 g. of ethyl 6-(4-benzylphenyl)-6-hydroxy-hexanoate as a yellow oil which was used in the subsequent reaction without further purification.

D. Preparation of ethyl 6-(4-benzylphenyl)-6-bromo-hexanoate.

A solution of 25.3 g. of phosphorous tribromide in 100 ml. of methylene chloride was added to a solution of 26.6 g. of ethyl 6-(4-benzylphenyl)-6-hydroxy-hexanoate in 400 ml. of methylene chloride that had previously been chilled to −10°C. The reaction was stirred for about 16 hours allowing the reaction to come to room temperature. The reaction was added to 6 liters of ice water which was then extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and evaporated *in vacuo* giving 26.1 g. of ethyl 6-(4-benzylphenyl)-6-bromo-hexanoate as a yellow oil.

E. Preparation of ethyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-6-(4-benzylphenyl)hexanoate.

A solution of 9.75 g. of ethyl 6-(4-benzylphenyl)-6-bromo-hexanoate, 5.03 g. of 2,4-dihydroxy-3-propylacetophenone, 3.57 g. of potassium carbonate, and 1.0 g. of potassium iodide in 175 ml. of acetone was heated to reflux for about 86 hours. The reaction was evaporated *in vacuo* and the residue was purified by chromatography over silica gel eluting with a 0—20% ethyl acetate gradient in hexane. The appropriate fractions were pooled and evaporated, giving 2.5 g. of the desired product which was used for the subsequent hydrolysis. NMR was consistent with the compound ethyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-6-(4-benzylphenyl)hexanoate.

F. Preparation of 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-6-(4-benzylphenyl)hexanoic acid.

A solution of 2.5 g. of ethyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-6-(4-benzylphenyl)hexanoate in 40 ml. of 1N sodium hydroxide and 20 ml. of ethanol was stirred for 24 hours. The reaction was diluted with 100 ml. of water, and was extracted with hexane and ethyl acetate. The aqueous layer was acidified with hydrochloric acid and extracted twice with ethyl acetate. The ethyl acetate layers were combined, dried over sodium sulfate, and evaporated *in vacuo* yielding 1.83 g. of the title product.

Analysis: $C_{30}H_{34}O_5$;
Calc.: C, 75.92; H, 7.22;
Found: C, 75.65; H, 7.31.

Example 16

6-(4-Acetyl-3-hydroxyphenoxy)-6-(4-benzylphenyl)hexanoic acid.

Following the procedure of Example 15, 3.75 g. of ethyl 6-(4-benzylphenyl)-6-bromo-hexanoate and 1.94 g. of 2,4-dihydroxyacetophenone were reacted to provide the intermediate ethyl hexanoate derivative which was then hydrolyzed to provide 0.95 g. of the title product as an oil.

Analysis: $C_{27}H_{28}O_5$;
Calc.: C, 74.98; H, 6.53;
Found: C, 74.75; H, 6.72.

Example 17

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-6-(4-biphenyl)hexanoic acid

Following the procedure of Example 15F the title product was prepared as an oil.

Analysis: $C_{29}H_{32}O_5$;
Calc.: C, 75.63; H, 7.00;
Found: C, 75.39; H, 7.17.

Example 18

6-(4-Acetyl-3-hydroxyphenoxy)-6-(4-biphenyl)hexanoic acid

Following the procedure of Example 17, using 2,4-dihydroxyacetophenone in place of 2,4-dihydroxy-3-propylacetophenone, the title compound was prepared, m.p. about 66—68°C.

Analysis: $C_{26}H_{26}O_5$;
Calc.: C, 74.62; H, 6.26;
Found: C, 74.82; H, 6.21.

Example 19

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-6-phenylhexanoic acid

Following the procedure of Example 15 using benzene in place of diphenylmethane, the title product was prepared as an oil.

Analysis: $C_{23}H_{28}O_5$;
Calc.: C, 71.85; H, 7.34;
Found: C, 71.59; H, 7.25.

Example 20

6-(4-Acetyl-3-hydroxyphenoxy)-6-phenylhexanoic acid

Following the procedure of Example 19, using 2,4-dihydroxyacetophenone in place of 2,4-dihydroxy-3-propylacetophenone, the title product was prepared, m.p. about 91—93°C.

Analysis: $C_{20}H_{22}O_5$;
Calc.: C, 70.16; H, 6.48;
Found: C, 70.00; H, 6.32.

Example 21

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)hexane nitrile

A solution of 44.4 g. of 2,4-dihydroxy-3-propylacetophenone, 42.2 g. of 6-chlorocapronitrile, 33.2 g. of potassium carbonate and 4.0 g. of potassium iodide in one liter of methyl ethyl ketone was allowed to reflux for three days. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. Chromatography of the residue over silica gel (0—30% ethyl acetate gradient in hexane) gave 53.6 g. of the title product as an oil.

Analysis: $C_{17}H_{23}NO_3$;
Calc.: C, 70.56; H, 8.01; N, 4.84;
Found: C, 70.34; H, 8.22; N, 5.13.

Example 22

5-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentyl]-tetrazole

Following the procedure of Example 8, 19.95 g. of 6-(4-acetyl-3-hydroxy-2-propylphenoxy)hexane nitrile were transformed into 12.7 g. of the title product, m.p. about 95—96°C.

Analysis: $C_{17}H_{24}N_4O_3$;
Calc.: C, 61.43; H, 7.28; N, 16.86;
Found: C, 61.34; H, 7.08; N, 16.72.

Example 23

5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]-tetrazole

The nitrile intermediate of the title compound was prepared following the procedure of Example 21 using 50.0 g. (257 mmoles) of 2,4-dihydroxy-3-propylacetophenone, 29.27 g. (282 mmoles) of 4-chlorobutyronitrile, 38.97 g. (282 mmoles) of potassium carbonate, and 4 g. of potassium iodide in 800 ml. of methyl ethyl ketone giving 57.58 g. of the nitrile intermediate as a rose-colored semi-crystalline solid. Twenty grams of the nitrile intermediate were then converted to the tetrazole in the usual manner giving 6.9 g. of the title compound, m.p. about 143—145°C.

Analysis: $C_{15}H_{20}N_4O_3$;
Calc.: C, 59.20; H, 6.62; N, 18.41;
Found: C, 58.96; H, 6.48; N, 18.49.

Example 24

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)hexanoic acid

The benzhydryl ester of 6-bromohexanoic acid was prepared *in situ* by reacting 14.6 g. (80 mmoles) of 6-bromohexanoic acid with 17.0 g. (88 mmoles) of diphenyldiazomethane in 200 ml. methylene chloride with a catalytic amount of boron trifluoride etherate. The methylene chloride was removed by evaporating *in vacuo* and the resulting oil was dissolved in 300 ml. of methyl ethyl ketone. To the resulting solution was added 15.5 g. (80 mmoles) of 2,4-dihydroxy-3-propylacetophenone, 11.0 g. (80 mmoles) of potassium carbonate, and 2 g. of potassium iodide. The reaction was allowed to reflux overnight. The reaction was then filtered, and the solvent removed *in vacuo*. The resulting oil was dissolved in 200 ml. of ethyl acetate and approximately 50 ml. of hexane was added. This organic solution was washed 3 times each with 250

ml. of dilute potassium carbonate solution. The organic phase was dried over sodium sulfate, filtered, and the solvent evaporated *in vacuo*. The product was purified by high pressure liquid chromatography (silica gel/0—20% ethyl acetate gradient in hexane) which after crystallization from hexane/ethyl acetate afforded 24.9 g. of diphenylmethyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-hexanoate.

Twenty grams of this benzhydryl ester were hydrolyzed by stirring in 150 ml. of formic acid and 10 ml. of triethylsilane for 2 days. The solvent was then removed *in vacuo* and the residue taken up into ethyl acetate/hexane. The organic solution was then extracted with 200 ml. of dilute potassium carbonate solution. The aqueous solution was then acidified with dilute hydrochloric acid and extracted with 200 ml. of ethyl acetate. The ethyl acetate solution was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from methylene chloride/hexane, giving 5.3 g. of the title product, m.p. about 63—64°C.

Analysis: $C_{17}H_{24}O_5$;
Calc.: C, 66.21; H, 7.85;
Found: C; 65.95; H, 7.63.

Examples 25—34

Following the procedure of Example 24, the following alkanoic acid derivatives were prepared using the appropriate phenols and bromoalkanoic acids. Yields are the molar yields based on the bromoalkanoic acid.

25. 6-(4-Acetyl-3-hydroxyphenoxy)hexanoic acid, m.p. about 130—131°C, 6% yield.
Analysis: $C_{14}H_{18}O_5$;
Calc.: C, 63.15; H, 6.81;
Found: C, 63.13; H, 6.92.

26. 6-(4-Acetyl-3-hydroxy-2-allylphenoxy)hexanoic acid, m.p. about 82—83°C, 16% yield.
Analysis: $C_{17}H_{22}O_5$;
Calc. C, 66.65; H, 7.24;
Found: C, 66.70; H, 7.02.

27. 4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butanoic acid, m.p. about 132—134°C, 21% yield.
Analysis: $C_{15}H_{20}O_5$;
Calc.: C, 64.27; H, 7.19;
Found: C, 64.02; H, 7.27.

28. 5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid, m.p. about 99—100°C, 1% yield.
Analysis: $C_{16}H_{22}O_5$;
Calc.: C, 65.29; H, 7.53;
Found: C, 65.16; H, 7.34.

29. 7-(4-Acetyl-3-hydroxy-2-propylphenoxy)heptanoic acid, m.p. about 59—60°C, 19% yield.
Analysis: $C_{18}H_{26}O_5$;
Calc.: C, 67.06; H, 8.13;
Found: C, 67.19; H, 7.93.

30. 8-(4-Acetyl-3-hydroxy-2-propylphenoxy)octanoic acid, m.p. about 77—78°C, 19% yield.
Analysis: $C_{19}H_{28}O_5$;
Calc.: C, 67.83; H, 8.39;
Found: C, 68.13; H, 8.40.

31. 9-(4-Acetyl-3-hydroxy-2-propylphenoxy)nonanoic acid, m.p. about 42—43°C, 24% yield.
Analysis: $C_{20}H_{30}O_5$;
Calc.: C, 68.55; H, 8.63;
Found: C, 68.69; H, 8.40.

32. 10-(4-Acetyl-3-hydroxy-2-propylphenoxy)decanoic acid, m.p. about 55—56°C, 26% yield.
Analysis: $C_{21}H_{32}O_5$;
Calc.: C, 69.20; H, 8.85;
Found: C, 69.54; H, 8.73.

33. 11-(4-Acetyl-3-hydroxy-2-propylphenoxy)undecanoic acid, m.p. about 58—59°C, 17% yield.
Analysis: $C_{22}H_{34}O_5$;
Calc.: C, 69.81; H, 9.05;
Found: C, 69.93; H, 8.94.

34. 6-(4-Acetyl-3-hydroxy-2-propylphenoxy)hexanoic acid, m.p. about 113—114°C, 19% yield.
Analysis: $C_{18}H_{26}O_5$;
Calc.: C, 67.06; H, 8.13;
Found: C, 66.23; H, 8.73.

Example 35

N-[6-(4-Acetyl-3-hydroxy-2-propylphenoxy)hexyl]morpholine hydrochloride

A solution of 10.7 g. (30 mmoles) of 6-(4-acetyl-3-hydroxy-2-propylphenoxy)hexyl bromide and 5.76 g. (66 mmoles) of morpholine in 100 ml. of dimethylformamide was stirred for 16 hours. The solvent was removed by evaporation and the residue was partitioned between 200 ml. of ethyl acetate and 200 ml. of

dilute hydrochloric acid. The aqueous layer was separated and then made basic with dilute potassium carbonate solution. The solution was extracted with ethyl acetate, and the ethyl acetate layer was separated, dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in 200 ml. of ether and gaseous hydrogen chloride was bubbled into the solution. The resulting precipitate was filtered to give 8.6 g. of the title product, m.p. about 157—159°C.

Analysis: $C_{21}H_{33}NO_4 \cdot HCl$;
Calc.: C, 63.02 H, 8.47; N, 3.50;
Found: C, 62.82; H, 8.35; N, 3.42.

Example 36

5-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)-1,1-dimethylpentyl]-tetrazole

A catalytic amount of ferric chloride was added to approximately 200 ml. of ammonia, followed by 1.84 g. (80 mmoles) of sodium metal. A solution of 3.64 ml. of isobutyronitrile in 50 ml. of ether was added to the ammonia solution in a dropwise manner over a period of 2 minutes. Five minutes after the addition was complete, a solution of 3.16 g. (40 mmoles) of 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl bromide in 50 ml. of ether was added over a 2 minute period. The reaction was stirred for 16 hours during which time the ammonia evaporated. The product was partitioned between ethyl acetate and dilute hydrochloric acid. The ethyl acetate was evaporated and the residue was purified by high pressure liquid chromatography to afford 5.6 g. of 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-1,1-dimethylhexyl nitrile.

Analysis: $C_{19}H_{27}NO_3$;
Calc.: C, 71.89; H, 8.57; N, 4.41;
Found: C, 72.14; H, 8.61; N, 4.19.

This nitrile intermediate (2.5 g.) was converted to the tetrazole according to the procedure of Example 8 to give 0.2 g. of the title compound, m.p. about 112—115°C.

Analysis: $C_{19}H_{28}N_4O_3$;
Calc.: C, 63.31; H, 7.83; N, 15.54;
Found: C, 63.33; H, 8.08; N, 15.75.

Example 37

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)heptanoic acid

Following the procedure of Example 15, ethyl 6-oxo-heptanoate was transformed into ethyl 6-bromoheptanoate. The reaction of 4.74 g. of ethyl 6-bromoheptanoate and 3.88 g. of 2,4-dihydroxy-3-propylacetophenone followed by hydrolysis in the usual manner gave 300 mg. of the title product as an oil.

Analysis: $C_{18}H_{26}O_5$;
Calc.: C, 67.06; H, 8.13;
Found: C, 66.03; H, 7.76

Example 38

6-(4-Acetyl-3-hydroxyphenoxy)heptanoic acid

Following the procedure of Example 37, 4.74 g. of ethyl 6-bromoheptanoate and 3.04 g. of 2,4-dihydroxyacetophenone were reacted in the usual manner and the resulting product hydrolyzed to give the title product, m.p. about 116-118°C.

Analysis: $C_{15}H_{20}O_5$;
Calc.: C, 64.27; H, 7.19;
Found: C, 64.15; H, 7.38

Example 39

5-[4-(4-Benzoyl-3-hydroxy-2-propylphenoxy)-butyl]-tetrazole

The title compound was prepared by first reacting 7.68 g. of 2,4-dihydroxy-3-propylbenzophenone with 4.86 g. of 5-bromovaleronitrile according to the procedure in Example 21. The reaction afforded 8.2 g. of the nitrile intermediate of the title compound. This nitril intermediate was then converted to the tetrazole following the procedure of Example 8 giving 1.2 g. of the title compound, m.p. about 114-115°C.

Analysis: $C_{21}H_2N_4O_3$;
Calc.: C, 66.30; H, 6.36;
Found: C, 66.15; H, 6.36

Example 40

Methyl 6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoate

A. *Preparation of methyl 6-bromo-2,2-dimethylhexanoate.*

To a solution of 5.0 g. of dry diisopropylamine in 60 ml. of dry tetrahydrofuran at −70°C were added dropwise via a syringe 32.6 ml. of a 1.5M solution of *n*-butyllithium in hexane. After stirring for about 20 minutes at −70°C, 6.0 g. of methyl isobutyrate were added and the reaction mixture allowed to stir at −70°C for about 40 minutes. A solution of 15.76 g. of 1,4-dibromobutane in a small volume of tetrahydrofuran was then added to the reaction mixture. The reaction mixture was slowly brought to room temperature over a period of about three hours. The reaction was quenched with 2.5 ml. of methanol. Fifty ml. of methylene

chloride were added followed by the addition of 50 ml. of 0.5N sodium hydroxide. The layers were separated and the aqueous phase was extracted with 50 ml. of methylene chloride. The combined organic layers were washed once with water, once with a saturated sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo* to give 14 g. of a pale yellow liquid, which was identified as methyl 6-bromo-2,2-dimethylhexanoate by NMR and IR.

B. Preparation of methyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoate.

Following the procedure of Example 15, 2.5 g. of methyl 6-bromo-2,2-dimethylhexanoate, 1.46 g. of potassium carbonate, a catalytic amount of potassium iodide, and 2.14 g. of 2,4-dihydroxy-3-propylacetophenone were reacted to give 2.96 g. of the title product as a brown oil. IR, NMR.

Example 41

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoic acid

A solution of 1.1 g. of methyl 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-2,2-dimethylhexanoate and 2.6 g. of lithium iodide in 50 ml. of collidine was heated to 100°C under a nitrogen blanket for about 46 hours. The reaction mixture was then added to ice. After making the solution acidic with hydrochloric acid, the solution was extracted with ether. The ether phase was washed three times with a 10% sodium bicarbonate solution. The ether solution was then further washed with a dilute hydrochloric acid solution, water, and a saturated sodium chloride solution. Evaporating the ether layer to dryness gave 1.03 g. of the title product, $M^+ = 336$; NMR.

Example 42

Methyl 6-(4-acetyl-3-hydroxyphenoxy)-2,2-dimethylhexanoate

Following the procedure of Example 40, 2.5 g. of methyl 6-bromo-2,2-dimethylhexanoate, 1.46 g. of potassium carbonate, a catalytic amount of potassium iodide, and 1.67 g. of 2,4-dihydroxyacetophenone were reacted in 125 ml. of acetone giving 2.3 g. of the title product as an oil. $M^+ = 308$; NMR.

Example 43

6-(4-Acetyl-3-hydroxyphenoxy)-2,2-dimethyl-hexanoic acid

Following the procedure of Example 41, 1.0 g. of methyl 6-(4-acetyl-3-hydroxyphenoxy)-2,2-dimethylhexanoate was hydrolyzed to give 0.86 g. of the title product. $M^+ = 294$; NMR.

Example 44

6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-nonanoic acid

Following the procedures of Examples 15E and 15F, 1.18 g. of methyl 6-bromo-nonanoate and 0.91 g. of 2,4-dihydroxy-3-propylacetophenone were reacted in the presence of 0.65 g. of potassium carbonate in 40 ml. of acetone. Hydrolysis of the ester intermediate with sodium hydroxide in aqueous ethanol gave the title product, $M^+ = 350$; NMR.

Example 45

6-(4-Acetyl-3-hydroxyphenoxy)nonanoic acid

Following the procedure of Example 44, 1.13 g. of methyl 6-bromo-nonanoate and 1.31 g. of 2,4-dihydroxy-acetophenone were reacted in 50 ml. of methyl ethyl ketone. Hydrolysis of the resulting methyl ester intermediate gave 0.3 g. of the title product, $M^+ = 308$; NMR, IR.

Examples 46-47

5-(1H)-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentyl]-1-tetrazolyacetic acid and 5-(2H)-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-2-tetrazolyl-acetic acid

A solution of 3.32 g. of 5-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-tetrazole, 1.38 g. of potassium carbonate, 0.5 g. of potassium iodide, and 1.67 g. of ethyl bromoacetate in 100 ml. of methyl ethyl ketone was allowed to reflux for 24 hours. The solvent was removed by evaporation and the residue was dissolved in 250 ml. of ethyl acetate. The solution was washed with 200 ml. of a saturated potasssium carbonate solution. The organic layer was evaporated to dryness and the residue was purified by chromatography over silica gel. Eight-tenths of a gram of a faster eluting material were recovered and characterized as the ethyl ester of the 2-substituted tetrazole product. The later eluting material weighed 1.0 g. and was characterized as the ethyl ester of the 1-substituted isomer. Each of the ester isomers was individually hydrolyzed according to the procedure of Example 15F giving the following products:

5-(1H)-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-1-tetrazolylacetic acid, 600 mg., m.p. about 148-149°C.

Analysis: $C_{19}H_{26}N_4O_5$;

Calc.: C, 58.45; H, 6.71; N, 14.35;

Found: C, 58.22; H, 7.00; N, 14.14.

5-(2H)-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-2-tetrazolylacetic acid, 500 mg., m.p. about 99-100°C.

Analysis: $C_{19}H_{26}N_4O_5$;
Calc.: C, 58.45; H, 6.71; N, 14.35;
Found: C, 58.18; H, 6.74; N, 14.13.

Example 48

1-Methyl-5-(1H)-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-tetrazole

A solution of 5 g. of 5-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-tetrazole, 3 g. of potassium carbonate, and 2.4 g. of methyl iodide in 250 ml. of methyl ethyl ketone was allowed to reflux overnight. The reaction mixture was treated with dilute hydrochloric acid and the layers were separated. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by chromatography over silica gel (2% ethanol in methylene chloride). The appropriate fractions were pooled and evaporated to an oil. Crystallization from ethyl acetate/hexane afforded 1.5 g. of the title product, m.p. about 72-75°C.

Analysis: $C_{18}H_{26}N_4O_3$;
Calc.: C, 62.41; H, 7.57; N, 16.17;
Found: C, 62.14; H, 7.40; N, 15.91.

Example 49

Alternate preparation of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid

The title product was prepared by heating 15.0 g. of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentane nitrile to reflux for six hours in 300 ml. of 2B ethanol and 40 ml. of 25% aqueous sodium hydroxide. The solution was evaporated to dryness and the residue was partitioned between diethyl ether and dilute sodium hydroxide solution. The aqueous layer was separated and acidified. The aqueous layer was extracted with ether. The ether extract was dried over sodium sulfate and evaporated to dryness. The residue was triturated with hexane and filtered to give 11 g. of the title product.

Example 50

Ethyl 5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentanoate

Eleven grams of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid were dissolved in 200 ml. of absolute ethanol. With stirring, 1 ml. of sulfuric acid was added and the reaction was stirred overnight. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate and dilute potassium carbonate solution. The ethyl acetate was separated, dried, and evaporated to give 9.9 g. of the title product, $M^+ = 322$.

Analysis: $C_{18}H_{26}O_5$;
Calc.: C, 67.06; H, 8.13;
Found: C, 66.43; H, 7.03.

Example 51

5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid amide

The acid chloride of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid was prepared by dissolving 9.3 g. of the acid in 150 ml. of methylene chloride followed by the addition of ten drops of dimethylformamide and 5.22 ml. of oxalyl chloride. After stirring at room temperature for one hour, the solvent was evaporated *in vacuo*. The residue was dissolved in benzene and evaporated *in vacuo*. The resulting acid chloride was dissolved in 100 ml. of methylene chloride and the solution was divided in half. One-half of the acid chloride solution was used in Example 56; the other half (50 ml.) of the acid chloride solution was added dropwise to 200 ml. of liquid ammonia. After stirring overnight, the solvent was evaporated and the residue was partitioned between dilute hydrochloric acid and ethyl acetate. The ethyl acetate solution was separated, washed once with dilute aqueous potassium carbonate, dried over sodium sulfate, filtered and evaporated to dryness. Crystallization from methylene chloride/hexane resulted in a total of 2.8 g. (two crops) of the title product, m.p. about 108-110°C.

Analysis: $C_{16}H_{23}NO_4$;
Calc.: C, 65.51; H, 7.90; N, 4.77;
Found: C, 65.30; H, 7.70; N, 4.47.

Example 52

N,N-dimethyl-5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid amide

The remaining 50 ml. of the methylene chloride/acid chloride solution from Example 51 were added to 50g. of dimethylamine in 100 ml. of methylene chloride. The reaction was worked up in the same manner as Example 51. Crystallization of the product from methylene chloride/hexane afforded 2.1 g. of the title product, m.p. about 95-97°C.

Analysis: $C_{18}H_{27}NO_4$;
Calc.: C, 67.26; H, 8.47; N, 4.36.
Found: C, 67.03; H, 8.23; N, 4.11.

Example 53

5-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)-butanethio]-tetrazole

A solution of 6.58 g. of 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl bromide, 3.04 g. of potassium carbonate, and 2.02 g. of 5-mercaptotetrazole in 50 ml. of dimethylformamide was stirred for 2 days at rom temperature. The reaction was evaporated to dryness *in vacuo* and the residue was dissolved in 150 ml. of ethyl acetate. The ethyl acetate was washed twice with 200 ml. each of dilute hydrochloric acid. The ethyl acetate solution was diluted with hexane to cloudiness and then extracted with 100 ml. of dilute potassium carbonate solution. The basic aqueous layer was then acidified with dilute hydrochloric acid and extracted with 250 ml. of ethyl acetate. The ethyl acetate layer was dried over sodium sulfate, filtered, and evaporated to dryness. The resulting residue was crystallized from methylene chloride/hexane to give 2.65 g. of the title product, m.p. about 80-81°C.

Analysis: $C_{16}H_{22}N_4O_3S$;
Calc.: C, 54.84; H, 6.33; N, 15.99;
Found: C, 54.57; H, 6.12; N, 16.08.

Examples 54-55

Following the procedure of Example 53, the following compounds were prepared using the appropriate bromide intermediates.

54. 5-[2-(4-Acetyl-3-hydroxy-2-propylphenoxy)ethanethio]-tetrazole, m.p. about 121-122°C.
Analysis: $C_{14}H_{18}N_4O_3S$;
Calc.: C, 52.16; H, 5.63; N, 17.38;
Found: C, 52.34; H, 5.11; N, 17.13.

55. 5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propanethio]-tetrazole, m.p. 129-130°C.
Analysis: $C_{15}H_{20}N_4O_3S$;
Calc.: C, 53.55; H, 5.99; N, 16.65;
Found: C, 53.91; H, 5.96; N, 16.39.

Example 56

S-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-propyl]-isothiuronium hydrobromide

A solution of 3.15 g. of 3-(4-acetyl-3-hydroxy-2-propylphenoxy)propyl bromide and 0.84 g. of thiourea in 100 ml. of ethanol was allowed to reflux for about three days. The solution was then evaporated *in vacuo* to a volume of about 50 ml. Diethyl ether was added until cloudy and the solution was placed in the freezer. A gum formed which was recovered by decantation. The mother liquor was again treated with ether to form a second gum. The mother liquor was evaporated to dryness. The two gums and the mother liquor residue were then each triturated with methylene chloride and the resulting residues were combined and crystallized from isopropanol/ether, to afford 0.8 g. of the title product, m.p. about 114-115°C.

Analysis: $C_{15}H_{22}N_2O_3S \cdot HBr$;
Calc.: C, 46.04; H, 5.92; N, 7.16; Br, 20.42;
Found: C, 47.95; H, 5.91; N, 6.85; Br, 20.80.

Example 57

5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentanehydroxamic acid

Four and six-tenths grams of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid were converted to the corresponding acid chloride according to the procedure of Example 51. The resulting acid chloride and 1.05 g. of hydroxylamine hydrochloride were dissolved in 50 ml. of methylene chloride, after which were added 4.15 ml. of triethylamine in about 50 ml. of methylene chloride. After stirring overnight at room temperature, the methylene chloride was removed by evaporation and the residue was partitioned between ethyl acetate and dilute hydrochloric acid. The layers were separated, and the ethyl acetate solution was evaporated *in vacuo*. The residue was dissolved in diethyl ether and the solution was extracted with dilute sodium hydroxide solution. The aqueous basic solution was then made acidic with dilute hydrochloric acid and the solution was extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate and evaporated to dryness. The residue was crystallized from methylene chloride/hexane to provide 400 mg. of the title product.

Analysis: $C_{16}H_{23}NO_5$;
Calc.: C, 62.12; H, 7.49; N, 4.53;
Found: C, 62.05; H, 7.40; N, 4.70.

Example 58

4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butane thiocyanate

To 10.65 g. of 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl bromide in 60 ml. of dry dimethylsulfoxide were added 6.5 g. of potassium thiocyanate. The solution was stirred overnight at room temperature and then was poured into water. The solution was extracted twice with dichloromethane. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered, and evaporated *in vacuo*.

The resulting oil was vacuum distilled to provide the title compound in 95% yield as a yellow viscous oil, b.p. about 205°C at 0.45 torr.

Analysis: $C_{16}H_{21}NO_3S$;

Calc.: C, 62.51; H, 6.89; N, 4.56; O, 15.61; S, 10.43

Found: C, 62.29; H, 6.61; N, 4.68; O, 15.71; S, 10.54.

Example 59-63

Following the procedure of Example 58, the following thiocyanate intermediates were prepared from the corresponding bromide intermediates.

59. 3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-propane thiocyanate, b.p. about 210°C at 0.25 torr, 76% yield.

Analysis: $C_{15}H_{19}NO_3S$;

Calc.: C, 61.41; H, 6.53; N, 4.77; O, 16.36; S, 10.93;

Found: C, 61.25; H, 6.50; N, 4.69; O, 16.33; S, 10.86.

60. 5-(4-Acetyl-3-hydroxy-2-propylphenoxy)-pentane thiocyanate, b.p. about 210°C at 0.6 torr, 92% yield.

Analysis: $C_{17}H_{23}NO_3S$;

Calc.: C, 63.52; H, 7.21; N, 4.36; O, 14.93; S, 9.98;

Found: C, 63.40; H, 7.29; N, 4.28; O, 14.89; S, 9.90.

61. 6-(4-Acetyl-3-hydroxy-2-propylphenoxy)-hexane thiocyanate, b.p. about 220°C at 0.4 torr, 87% yield.

Analysis: $C_{18}H_{25}NO_3S$;

Calc.: C, 64.44; H, 7.51; N, 4.18; O, 14.31; S, 9.56;

Found: C, 64.31; H, 7.71; N, 4.00; O, 14.22; S, 9.36.

62. 7-(4-Acetyl-3-hydroxy-2-propylphenoxy)-heptane thiocyanate, b.p. about 224°C at 0.5 torr, 81% yield.

Analysis: $C_{19}H_{27}NO_3S$;

Calc.: C, 65.29; H, 7.79; N, 4.01; O, 13.73; S, 9.18;

Found: C, 65.18; H, 8.07; N, 3.97; O, 13.79; S, 9.97.

63. 8-(4-Acetyl-3-hydroxy-2-propylphenoxy)-octane thiocyanate, b.p. about 234°C at 0.25 torr, 89% yield.

Analysis: $C_{20}H_{29}NO_3S$;

Calc.: C, 66.08; H, 8.04; N, 3.85; O, 13.20; S, 8.82;

Found: C, 65.86; H, 7.88; N, 3.67; O, 13.26; S, 8.63.

Example 64

5-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)-pentanethio]-tetrazole

To 5.8 g. (18 mmoles) of 5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentane thiocyanate in 70 ml. of dry dimethylformamide were added 36 mmoles of ammonium chloride and 72 mmoles of sodium azide. The resulting suspension was heated overnight at about 80°C. After cooling, the solution was quenched with water and the resulting suspension was acidifed with hydrochloric acid. The mixture was extracted three times with chloroform and the combined chloroform extracts were back-extracted with 20% aqueous sodium hydroxide. After washing the basic solution once with chloroform, the solution was acidified with hydrochloric acid. The resulting precipitate was collected by filtration and crystallized from methanol to give a 78% yield of the title product, m.p. about 96—98°C.

Analysis: $C_{17}H_{24}N_4O_3S$;

Calc.: C, 56.02; H, 6.64; N, 15.37; O, 13.17; S, 8.80;

Found: C, 55.88; H, 6.89; N, 15.55; O, 13.00; S, 7.95;

Examples 65—69

Following the procedure of Example 64, the following products were prepared from the corresponding thiocyanate intermediates.

65. 5-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propanethio]-tetrazole, m.p. about 131—133°C, 74% yield.

Analysis: $C_{15}H_{20}N_4O_3S$;

Calc.: C, 53.55; H, 5.99; N, 16.66; O, 14.27; S, 9.53;

Found: C, 53.33; H, 5.85; N, 16.36; O, 14.47; S, 9.23.

66. 5-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butanethio]-tetrazole, m.p. about 84—86°C, 79% yield.

Analysis: $C_{16}H_{22}N_4O_3S$;

Calc.: C, 54.84; H, 6.33; N, 15.99; O, 13.70; S, 9.15;

Found: C, 54.63; H, 6.10; N, 15.96; O, 13.78; S, 8.85.

67. 5-[6-(4-Acetyl-3-hydroxy-2-propylphenoxy)hexanethio]-tetrazole, m.p. about 85—87°C, 54% yield.

Analysis: $C_{18}H_{26}N_4O_3S$;

Calc.: C, 57.12; H, 6.93; N, 14.81; O, 12.68; S, 8.47;

Found: C, 56.89; H, 6.86; N, 14.64; O, 12.43; S, 8.22.

68. 5-[7-(4-Acetyl-3-hydroxy-2-propylphenoxy)heptanethio]-tetrazole, m.p. about 84—86°C, 65% yield.
Analysis: $C_{19}H_{28}N_4O_3S$;
Calc.: C, 58.14; H, 7.19; N, 14.28; O, 12.27; S, 8.17;
Found: C, 57.89; H, 6.91; N, 14.33; O, 12.09; S, 8.09.

69. 5-[8-(4-Acetyl-3-hydroxy-2-propylphenoxy)octanethio]-tetrazole, m.p. about 66—68°C, 38% yield.
Analysis: $C_{20}H_{30}N_4O_3S$;
Calc.: C, 59.08; H, 7.44; N, 13.78; O, 11.81; S, 7.89;
Found: C, 59.31; H, 7.51; N, 13.66; O, 11.61; S, 7.65.

Example 70

5-[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentanesulfonyl)-tetrazole

To a solution of 1.8 g. of 5-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanethio]-tetrazole in 20 ml. of glacial acetic acid were added 5 ml. of 30% hydrogen peroxide. The solution was heated at 60°C for about five hours. The cooled solution was evaporated under reduced pressure, water was added, and the mixture was extracted with dichloromethane. The organic extract was dried over magnesium sulfate, filtered, and evaporated *in vacuo* to give the title product as a yellow oil.

The compounds of Formula I (provided R_4 is not cyano or cyanothio) should be useful in treating any condition, including clinical conditions, which is characterized by excessive release of leukotrienes C_4, D_4, or E_4. These conditions include immediate type hypersensitivity reactions such as asthma. Evidence obtained over the past few years has shown the presence of leukotrienes in sputum of patients with chronic bronchitis (Turnbull, *et al, Lancet II*, 526 (1977)) and cystic fibrosis (Cromwell, *et al., Lancet II*, 164 (1981)), suggesting a role of leukotrienes in the pathology of those diseases. Furthermore, Lewis and colleagues [*Int. J. Immunopharmacology, 4*, 85 (1982)] have recently detected material in rheumatoid synovial fluid that reacts antigenically with antibody to LTD_4. This may hallmark the existence of leukotriene permeability factors that, together with LTB_4, augment the inflammatory process in the diseased joints. Therefore, the compounds described in this invention should also alleviate some of the symptoms of chronic bronchitis and cystic fibrosis and possibly rheumatoid arthritis by virtue of their ability to antagonize leukotrienes.

In addition, some of the compounds of Formula I have demonstrated lipoxygenase activity which further suggests the use of these compounds as anti-inflammatory agents.

SRS—A or leukotriene antagonism was demonstrated by the following test procedure:

Male, Hartley guinea pigs weighing 200—450 grams were killed by decapitation. A section of terminal ileum was removed, the lumen cleaned, and the tissue divided into 2.5 cm. segments. The ilea were mounted in 10 ml. tissue baths containing Krebs-bicarbonate solution of the following composition in mmoles/-liter: KCl, 4.6; $CaCl_2$—$\cdot 2H_2O$, 1.2; KH_2PO_4, 1.2; $MgSO_4 \cdot 7H_2O$, 1.2; NaCl, 118.2; $NaHCO_3$, 24.8 and dextrose, 10.0. The bath fluid was maintained at 37°C and aerated with 95 percent oxygen and 5 percent CO_2. In addition, the buffer contained 1×10^{-6}M atropine to reduce ileal spontaneous activity. In studies with crude SRS—A, 1×10^{-6}M pyrilamine was used to mitigate the actions of histamine present along with the biologically active leukotrienes. Isometric measurements were made with a Grass FTO3C force-displacement transducer and recorded on a Grass polygraph as change in grams of force. A passive force of 0.5 g. was applied to the tissues. After an appropriate equilibration period, single submaximal control responses to either SRS—A or pure LTD_4 were obtained. Following a 5 minute exposure of the ileum to an experimental drug, the control concentration of SRS—A or LTD_4 was added to the tissue bath. The response of the ileum to SRS—A or LTD_4 in the presence of the drug was compared to the response in the absence of the drug.

For some of the drugs in this seris a more detailed analysis of LTD_4 antagonism was made. In these experiments, cumulative concentration-response curves were obtained to LTD_4 in guinea pig ileum and trachea. This was followed by a 30 minute incubation with various concentrations of the experimental drug. The concentration response curve to LTD_4 was then repeated in the presence of the antagonist. Only one concentration of antagonist was used on a single tissue. K_B values were calculated by the method of Furchgott [*Ann. N.Y. Acad. Sci., 139*, 553 (1967)] using the following equation.

$$K_B = \frac{[\text{Antagonist}]}{\text{Dose Ratio} - 1}$$

Dose ratio refers to the concentration of agonist required to elicit 50 percent of the maximal response (ED_{50}) in the presence of the antagonist divided by the ED_{50} in the absence of the antagonist. Calculations were performed with the aid of a computer and a digital plotter. The compounds of Formula I showed varying degrees of leukotriene antagonist activity when assayed on the isolated guinea pig ileum as summarized in Table I;

TABLE 1

Percent Inhibition of LTD_4 or SRS—A*
evoked ileal contractions

Compound of Example No.	Compound concentration			
	1×10^{-5}M	3×10^{-6}M	1×10^{-6}M	pA_2
8		100	89	7.2
9		100	87	7.1
10		95	92	7.1
11		100	89	6.5
12		90	78	6.5
13		93	76	6.5
14		47	22	
15	37			
16	86	70		
17*	44			
18		34		
19	64	35		
20*		20		
22		87		6.58
23			15	
24		81		6.4
25*		11		
26		29		
28*		61		5.8
29	84		43	
30	94		62	
31	94		51	5.7
32	92	85	46	
33	92	79		

TABLE 1 continued

Compound of Example No.	Compound concentration			
	1×10^{-5}M	3×10^{-6}M	1×10^{-6}M	pA_2
34	88	56		6.1
35	80	47		
36			89	
37	79	45		5.8
38		10		
39		56	34	
40		55		
41	94	73		
42	23			
43	22			
44	34			
45	18			
46			66	
47			69	
48			38	
50		56	40	
51		59	28	
52		42	17	
53			87	7.0
54			47	5.95
55			95	7.5
56		55	28	
57		70	28	
64	100		82	6.8
67	100		95	
68			100	
69	100		50	6.3

*Compounds marked with an asterisk were tested using crude SRS—A as the ileum-contracting agent; all other compounds were tested using pure LTD_4.

The compounds or formulations of the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g. by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injection solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injection solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from 5 to 500 mg. (from 5.0 to 50 mg. in the case of parenteral or inhalation administration, and from 25 to 500 mg. in the case of oral or rectal administration) of a compound of Formula I. Dosages of from 0.5 to 300 mg./kg. per day, preferably 0.5 to 20 mg./kg., of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The formulations of the present invention normally will consist of at least one compound of formula I (provided R_4 is not cyano or cyanothio) mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therepeutic substance.

Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorofluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention are capsules, tablets, suppositories, injectable solutions, creams and ointments. Especially preferred are formulations for inhalation application, such as an aerosol, and for oral ingestion.

Additional Characterizing Data

Example 1B, NMR (DMSO) δ: 13.0 (s, 1H), 7.9 (d, 1H), 6.7 (d, 1H), 4.2 (t, 2H), 2.8 (t, 2H), 2.7 (s, 3H), 2.6 (t, 2H), 2.2—1.2 (m, 6H), 1.0 (t, 3H).

Example 2, NMR ($CDCl_3$) δ: 12.8 (s, 1H), 7.6 (d, 1H), 6.5 (d, 1H), 4.1 (t, 2H), 2.8 (t, 2H), 2.7 (s, 3H), 2.5 (t, 2H), 2.1—1.3 (m, 10H), 1.0 (t, 3H).

Example 4, NMR (DMSO) δ: 13.0 (s, 1H), 7.9 (d, 1H), 6.7 (d, 1H), 4.1 (t, 2H), 2.8 (t, 2H), 2.7 (s, 3H), 2.6 (t, 2H), 2.1—1.2 (m, 14H), 1.0 (t, 3H).

Example 5, NMR ($CDCl_3$) δ: 12.65 (s, 1H), 7.50 (d, 1H), 6.35 (d, 1H), 3.93 (t, 2H), 2.52 (t, 2H), 2.45 (s, 3H), 2.22 (t, 2H), 1.8—1.1 (m, 16H), .85 (t, 3H).

Example 6, NMR (DMSO) δ: 12.85 (s, 1H), 7.8 (d, 1H), 6.65 (d, 1H), 4.1 (t, 2H), 2.75 (t, 2H), 2.65 (s, 3H), 2.5 (t, 2H), 2.1—1.2 (m, 18H), .95 (t, 3H).

Example 7, NMR (DMSO) δ: 12.9 (s, 1H), 7.9 (d, 1H), 6.7 (d, 1H), 4.2 (t, 2H), 2.9 (t, 2H), 2.7 (s, 3H), 2.55 (t, 2H), 2.1—1.2 (m, 22H), 1.0 (t, 3H).

Example 15F, NMR ($CDCl_3$) δ: 12.9 (s, 1H), 10.6 (s, 1H), 7.3 (d, 1H), 7.2—7.0 (m, 9H), 6.2 (d, 1H), 5.1 (t, 1H), 3.9 (s, 2H), 2.7 (t, 2H), 2.4 (s, 3H), 2.3 (t, 2H), 2.1—1.2 (m, 8H), .97 (t, 3H).

Example 16, NMR ($CDCl_3$) δ: 7.45 (d, 1H), 7.3—7.0 (m, 9H), 6.4 (d, 1H), 6.25 (d, 1H), 5.2 (t, 1H), 3.9 (s, 2H), 2.47 (s, 3H), 2.3 (t, 2H), 2.1—1.25 (m, 6H).

Example 17, NMR ($CDCl_3$) characteristic shifts δ:

$$5.3\ (t,\ 1H,\ O\text{—}\underset{\substack{|\\ Ar}}{CH}\text{—}CH_2),$$

6.3 (d, 1H, Ar-H meta to acetyl), 12.8 (s, 1H, ArOH).

Example 19, NMR ($CDCl_3$) δ: 0.97 (t, 3H), 1.4—1.7 (m, 4H), 1.88 (m, 2H), 2.01 (m, 2H), 2.32 (t, 2H), 2.44 (s, 3H), 2.72 (t, 2H), 5.21 (t, 1H), 6.17 (d, 1H), 7.2—7.4 (m, 5H), 7.37 (d, 1H), 12.72 (s, 1H).

Example 21, NMR ($CDCl_3$) δ: 0.93 (t, 3H), 1.53 (quint, 2H), 1.70 (m, 4H), 1.84 (t, 2H), 2.40 (t, 2H), 2.56 (s, 3H), 2.62 (t, 2H), 4.05 (t, 2H), 6.41 (d, 1H), 7.58 (d, 1H), 12.76 (s, 1H).

Example 36, 6-(4-acetyl-3-hydroxy-2-propylphenoxy)-1,1-dimethylhexyl nitrile, NMR ($CDCl_3$) δ: 0.96 (t, 3H), 1.38 (s, 6H), 1.5—1.8 (m, 6H), 1.96 (m, 2H), 2.58 (s, 3H), 2.64 (t, 2H), 4.06 (t, 2H), 6.42 (d, 1H), 7.59 (d, 1H), 12.74 (s, 1H).

Example 32, NMR ($CDCl_3$) δ: 0.88 (t, 3H), 1.21 (d, 3H), 1.46 (m, 4H), 1.60 (m, 4H), 2.34 (t, 2H), 2.52 (s, 3H), 2.58 (t, 2H), 4.48 (m, 1H), 6.37 (d, 1H), 7.54 (d, 1H), 12.76 (s, 1H).

Example 40B, NMR ($CDCl_3$) δ: 12.7 (s, 1H), 7.7 (d, 1H), 6.5 (d, 1H), 4.0 (t, 2H), 3.7 (s, 3H), 2.8—1.6 (m, 13H), 1.1 (s, 6H), 1.0 (t, 3H).

Example 41, NMR ($CDCl_3$) δ: 12.7 (s, 1H), 7.75 (d, 1H), 6.4 (d, 1H), 4.0 (t, 2H), 2.6 (t, 2H), 2.55 (s, 3H), 1.4—1.9 (m, 6H), 1.1 (s, 6H), 0.9 (t, 3H).

Example 42, NMR ($CDCl_3$) δ: 12.7 (s, 1H), 7.7 (d, 1H), 6.5 (m, 3H), 4.0 (t, 2H), 3.7 (s, 3H), 1.3—2.0 (m, 6H), 1.1 (s, 6H).

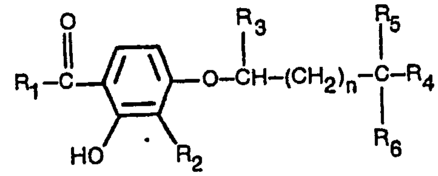
Example 43, NMR ($CDCl_3$) δ: 12.7 (s, 1H), 7.6 (d, 1H), 6.4 (m, 2H), 4.0 (t, 2H), 2.5 (s, 3H), 1.9—1.3 (m, 6H), 1.1 (s, 6H).

Example 44, NMR ($CDCl_3$) δ: 12.8 (s, 1H), 7.6 (d, 1H), 6.45 (d, 1H), 4.4 (m, 1H), 2.7 (t, 2H), 2.6 (s, 3H), 2.3 (t, 2H), 1.8—1.3 (m, 12H), 0.9 (m, 6H).

Example 45, NMR ($CDCl_3$) δ: 12.7 (s, 1H), 76 (d, 1H), 6.4 (m, 2H), 4.3 (m, 1H), 2.5 (s, 3H), 2.3 (t, 2H), 1.8—1.2 (m, 8H), 0.9 (t, 3H).

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula I

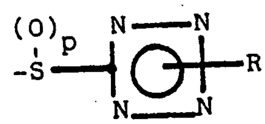


I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, C_1—C_6 alkyl or C_3—C_8 cycloalkyl;
R_2 is hydrogen, C_1—C_6 alkyl, or C_2—C_6 alkenyl;
R_3 is hydrogen, C_1—C_{10} alkyl, phenyl, C_1—C_{10} alkyl-substituted phenyl, biphenyl, or benzylphenyl;
R_4 is —$COOR_7$, —$CONR_8R_9$, —CONHOH, —SC(=NH)NH_2, cyano, thiocyanato,

or



where

R_7 is hydrogen or C_1—C_4 alkyl,
R_8 and R_9 are each independently hydrogen, C_1—C_3 alkyl, or when taken together with the nitrogen atom form a morpholine or N-methyl piperazine ring,
R is hydrogen, C_1—C_4 alkyl, or —CH_2COOR_7, and p is 0, 1, or 2;
R_5 and R_6 are each independently hydrogen or C_1—C_3 alkyl; and n is 0—10;

provided that (a) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is —$COOCH_3$, n is 0 to 2 or 4—10, and (b) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is —$COOC_2H_5$, n is 0 or 2—10.

2. A compound of the formula I as shown in claim 1 or a pharmaceutically acceptable salt thereof, wherein R_1 is C_1—C_6 alkyl, R_2 is C_1—C_6 alkyl or C_3—C_6 alkenyl, R_3 is hydrogen, R_5 is hydrogen, R_6 is hydrogen, R_4 is —COOH, 5-tetrazolyl or 5-thiotetrazolyl and n is 1—4.

3. A compound of claim 1 wherein R_1 is methyl and R_2 is propyl.

4. A compound of claim 1 or 3 wherein n is 1—4.

5. A compound of claim 1, 3, or 4 wherein R_4 is —COOH, 5-tetrazolyl or 5-tetrazolylthio.

6. A compound selected from 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butanoic acid or a pharmaceutically acceptable salt thereof,

5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid or a pharmaceutically acceptable salt thereof,

6-(4-acetyl-3-hydroxy-2-propylphenoxy)hexanoic acid or a pharmaceutically acceptable salt thereof,

5-[4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl]-tetrazole or a pharmaceutically acceptable salt thereof,

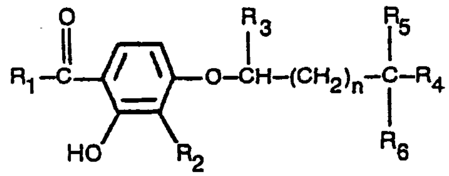
5-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-tetrazole or a pharmaceutically acceptable salt thereof,

5-[6-(4-acetyl-3-hydroxy-2-propylphenoxy)hexyl]-tetrazole or a pharmaceutically acceptable salt thereof,

5-[4-(4-acetyl-3-hydroxy-2-propylphenoxy)butanethio]-tetrazole or a pharmaceutically acceptable salt thereof, or

5-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propanethio]-tetrazole or a pharmaceutically acceptable salt thereof.

7. A compound of formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

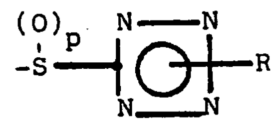
R_1 is hydrogen, C_1—C_6 alkyl or C_3—C_8 cycloalkyl;

R_2 is hydrogen, C_1—C_6 alkyl, C_2—C_6 alkenyl;

R_3 is hydrogen, C_1—C_{10} alkyl, phenyl, C_1—C_{10} alkyl-substituted phenyl, biphenyl, or benzylphenyl;

R_4 is —$COOR_7$, —$CONR_8R_9$, —CONHOH, —SC(=NH)NH_2,

or



where R_7 is hydrogen or C_1—C_4 alkyl,

R_8 and R_9 are each independently hydrogen, C_1—C_3 alkyl, or when taken together with the nitrogen atom form a morpholine or N-methyl piperazine ring,

R is hydrogen, C_1—C_4 alkyl, or —CH_2COOR_7, and p is 0, 1, or 2;

R_5 and R_6 are each independently hydrogen or C_1—C_3 alkyl;

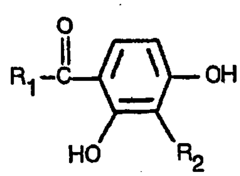
and n is 0—10; for use as a pharmaceutical.

8. A compound of formula (I) as defined in any one of claims 1—4, provided R_4 is not cyano or thiocyanato, for use as a leukotriene antagonist.

9. A compound of claim 6 for use in treatment of allergic disorder.

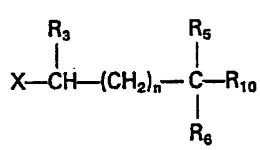
10. A process for preparing a compound of the formula I as defined in claim 1, which comprises

a) reacting a compound of formula (II)



II

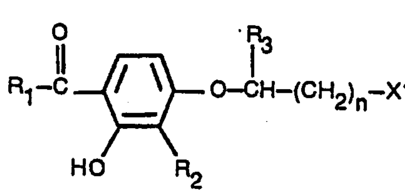
wherein R_1 and R_2 are as defined in claim 1, with a compound of formula (III)



(III)

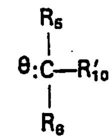
where R_3, R_5, R_6 and n are as defined in formula (I), X is a leaving group, and R_{10} is cyano, thiocyanato, or —$COOR_7$, where R_7 is as defined in formula (I), to provide a compound of formula (I) wherein R_4 is cyano, cyanothio, or —$COOR_7$; or

b) reacting a compound of formula



V'

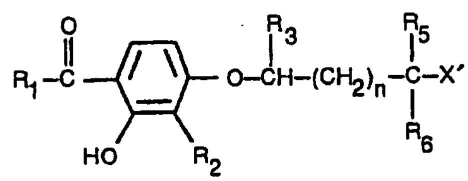
where R_1, R_2, R_3, and n are as defined in formula (I) and X' is a leaving group, with a source of a carbanion of the formula



(VII')

where R_5 and R_6 are as defined in formula (I) and R'_{10} is cyano or $COOR_7$, where R_7 is C_1—C_4 alkyl, to provide a compound of formula (I) wherein R_4 is cyano or $COOR_7$; or

c) reacting a compound of formula (V)



V

where R_1, R_2, R_3, R_5 and R_6 are as defined in formula (I) and X' is a leaving group, with

1) an alkali metal cyanide to provide a compound of formula (I) wherein R_4 is cyano, or

2) an alkali metal thiocyanate to provide a compound of formula (I) wherein R_4 is thiocyanato, or

3) thiourea to provide a compound of formula (I) wherein R_4 is —SC(=NH)NH_2, or

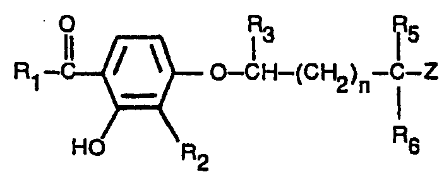
4) 5-mercaptotetrazole to provide a compound of formula (I) wherein R_4 is tetrazolylthio; or

d) hydrolyzing a compound of formula (I) wherein R_4 is cyano to provide a compound of formula (I) wherein R_4 is carboxyl, or

e) reacting a compound of formula (I) wherein R_4 is cyano with an alkali metal azide and ammoniumchloride to provide a compound of formula (I) wherein R^4 is 5-tetrazolyl; or

f) reacting a compound of formula (I) wherein R_4 is thiocyanato with an alkali metal azide and ammoniumchloride to provide a compound of formula (I) wherein R_4 is tetrazolylthio,

g) reacting a compound of formula (VIII)



(VIII)

wherein R_1, R_2, R_3, R_5, R_6 are as defined in formula (I) and Z is a protected acid ester or —COCl

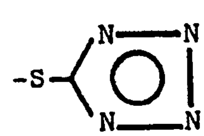
1) with water to provide a compound of formula (I) wherein R_4 is carboxyl, or

2) with HNR_8R_9, where R_8 and R_9 are as defined in formula (I) to provide a compound of formula (I) wherein R_4 is $CONR_8R_9$, or

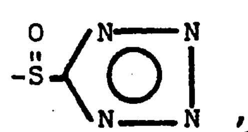
3) with H_2NOH to provide a compound of formula (I) wherein R_4 is —CONHOH; or

h) esterifying a compound of formula (I) wherein R_4 is carboxyl to provide a compound of formula (I) wherein R_4 $COOR_7$' where R_7' is C_1—C_4 alkyl, or

i) reacting a compound of formula (I) wherein R_4 is

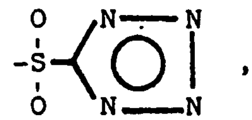


1) with a mild oxidizing agent to produce a compound of formula (I) wherein R_4 is

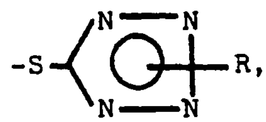


or

2) with a strong oxidizing agent to provide a compound of formula (I) wherein R_4 is

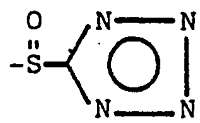


3) with an alkyl halide or alkyl haloacetate to provide a compound of formula (I) wherein R_4 is

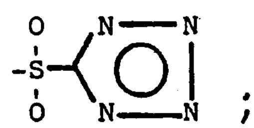


when R is as defined in formula (I); or

j) reacting a compound of formula (I) wherein R_4 is



with a strong oxidizing agent to provide a compound of formula (I) wherein R_4 is



k) reacting a compound of formula (I) wherein R_4 is

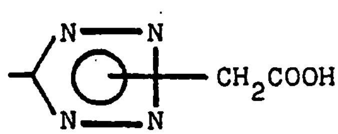
with an alkyl halide or an alkyl halo acetate to provide a compound of formula (I) wherein R_4 is

where R is C_1—C_4 alkyl or —CH_2COOR_7 where R_7 is C_1—C_4 alkyl; or

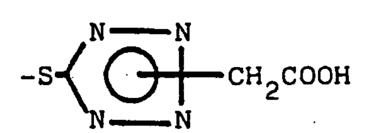
l) hydrolyzing a compound of formula (I) wherein R_4 is

or

where R_7 is C_1—C_4 alkyl to provide a compound of formula (I) wherein R_4 is



or

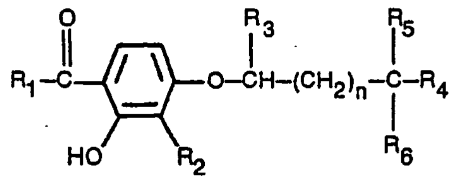


or

m) salifying a compound of formula (I).

Claims for the Contracting State: AT

1. A process for preparing a compound of the formula I

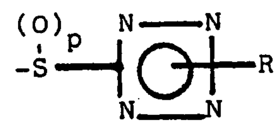


I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, C_1—C_6 alkyl or C_3—C_8 cycloalkyl;
R_2 is hydrogen, C_1—C_6 alkyl, or C_2—C_6 alkenyl;
R_3 is hydrogen, C_1—C_{10} alkyl, phenyl, C_1—C_{10} alkyl-substituted phenyl, biphenyl, or benzylphenyl;
R_4 is —$COOR_7$, —$CONR_8R_9$, —CONHOH, —SC(=NH)NH_2, cyano, thiocyanato,

or

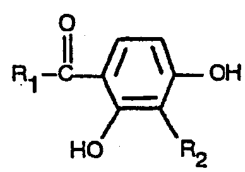


where

R_7 is hydrogen or C_1—C_4 alkyl,
R_8 and R_9 are each independently hydrogen, C_1—C_3 alkyl, or when taken together with the nitrogen atom form a morpholine or N-methyl piperazine ring,
R is hydrogen, C_1—C_4 alkyl, or —CH_2COOR_7, and p is 0, 1, or 2;
R_5 and R_6 are each independently hydrogen or C_1—C_3 alkyl; and n is 0—10;

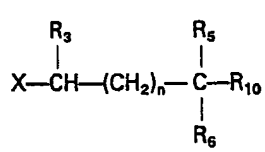
provided that (a) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is —$COOCH_3$, n is 0 to 2 or 4—10, and (b) when R_1 is CH_3, R_2 is C_3H_7, R_3 is hydrogen, R_5 and R_6 are both hydrogen and R_4 is —$COOC_2H_5$, n is 0 or 2—10; which comprises

a) reacting a compound of formula (II)



II

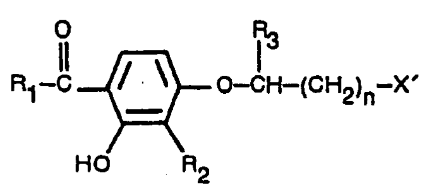
with a compound of formula (III)



(III)

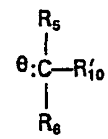
where R_3, R_5, R_6 and n are as defined in formula (I), X is a leaving group, and R_{10} is cyano, thiocyanato, or —$COOR_7$, where R_7 is as defined in formula (I), to provide a compound of formula (I) wherein R_4 is cyano, thiocyanato, or —$COOR_7$; or

b) reacting a compound of formula



V'

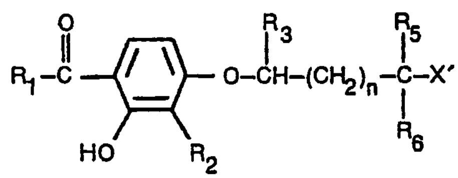
where R_1, R_2, R_3, and n are as defined in formula (I) and X' is a leaving group, with a source of a carbanion of the formula



(VII')

where R_5 and R_6 are as defined in formula (I) and R'_{10} is cyano or $COOR_7$, where R_7 is as defined in formula (I), to provide a compound of formula (I) wherein R_4 is cyano or $COOR_7$; or

c) reacting a compound of formula (V)



V

where R_1, R_2, R_3, R_5 and R_6 are as defined in formula (I) and X' is a leaving group, with

1) an alkali metal cyanide to provide a compound of formula (I) wherein R_4 is cyano, or

2) an alkali metal thiocyanate to provide a compound of formula (I) wherein R_4 is thiocyanato, or

3) thiourea to provide a compound of formula (I) wherein R_4 is —SC(=NH)NH_2, or

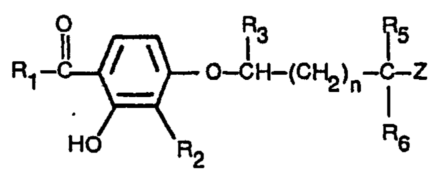
4) 5-mercaptotetrazole to provide a compound of formula (I) wherein R_4 is tetrazolylthio; or

d) hydrolyzing a compound of formula (I) wherein R_4 is cyano to provide a compound of formula (I) wherein R_4 is carboxyl, or

e) reacting a compound of formula (I) wherein R_4 is cyano with an alkali metal azide and ammoniumchloride to provide a compound of formula (I) wherein R_4 is 5-tetrazolyl; or

f) reacting a compound of formula (I) wherein R_4 is cyanothio with an alkali metal azide and ammoniumchloride to provide a compound of formula (I) wherein R_4 is tetrazolylthio,

g) reacting a compound of formula (VIII)



(VIII)

wherein R_1, R_2, R_3, R_5, R_6 are as defined in formula (I) and Z is a protected acid ester or —COCl

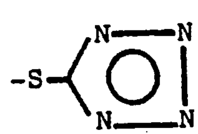
1) with water to provide a compound of formula (I) wherein R_4 is carboxyl, or

2) with HNR_8R_9, where R_8 and R_9 are as defined in formula (I) to provide a compound of formula (I) wherein R_4 is $CONR_8R_9$, or

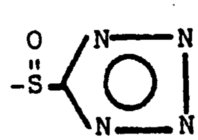
3) with H_2NOH to provide a compound of formula (I) wherein R_4 is —CONHOH; or

h) esterifying a compound of formula (I) wherein R_4 is carboxyl to provide a compound of formula (I) wherein R_4 is $COOR_7'$, or

i) reacting a compound of formula (I) wherein R_4 is

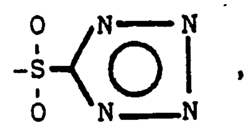


1) with a mild oxidizing agent to produce a compound of formula (I) wherein R_4 is

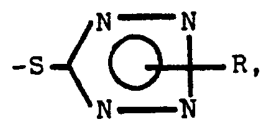


or

2) with a strong oxidizing agent to provide a compound of formula (I) wherein R_4 is

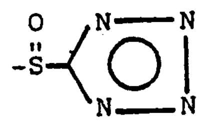


3) with an alkyl halide or alkyl haloacetate to provide a compound of formula wherein R_4 is

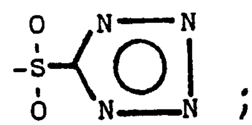


when R is as defined in formula (I); or

j) reacting a compound of formula (I) wherein R_4 is

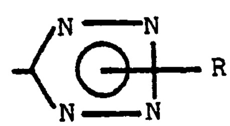


with a strong oxidizing agent to provide a compound of formula (I) wherein R_4 is



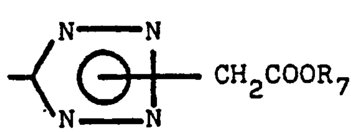
k) reacting a compound of formula (I) wherein R_4 is

with an alkyl halide or an alkyl halo acetate to provide a compound of formula (I) wherein R_4 is



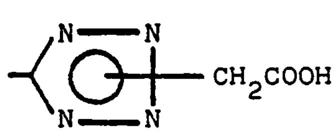
where R is C_1—C_4 alkyl or —CH_2COOR_7 where R_7 is C_1—C_4 alkyl; or

l) hydrolyzing a compound of formula (I) wherein R_4 is

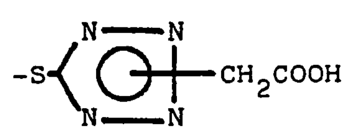


or

where R_7 is C_1—C_4 alkyl to provide a compound of formula (I) wherein R_4 is



or



or

m) salifying a compound of formula (I).

2. A process of claim 1 for preparing a compound of formula (I) wherein R_1 is methyl and R_2 is propyl.

3. A process of claim 1 or 2 for preparing a compound of formula (I) wherein n is 1—4.

4. A process of claim 1, 2, or 3 for preparing a compound of formula (I) wherein R_4 is —COOH, 5-tetrazolyl or 5-tetrazolylthio.

5. A process of claim 1 for preparing a compound selected from 4-(4-acetyl-3-hydroxy-2-propylphenoxy)butanoic acid or a pharmaceutically acceptable salt thereof,

5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentanoic acid or a pharmaceutically acceptable salt thereof,

6-(4-acetyl-3-hydroxy-2-propylphenoxy)hexanoic acid or a pharmaceutically acceptable salt thereof,

5-[4-(4-acetyl-3-hydroxy-2-propylphenoxy)butyl]-tetrazole or a pharmaceutically acceptable salt thereof,

5-[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]-tetrazole or a pharmaceutically acceptable salt thereof,

5-[6-(4-acetyl-3-hydroxy-2-propylphenoxy)hexyl]-tetrazole or a pharmaceutically acceptable salt thereof,

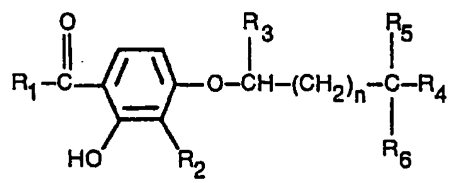
5-[4-(4-acetyl-3-hydroxy-2-propylphenoxy)butanethio]-tetrazole or a pharmaceutically acceptable salt thereof, or

5-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)propanethio]-tetrazole or a pharmaceutically acceptable salt thereof.

6. A compound of formula (I) whenever prepared by the process of any one of claims 1—5.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel (I)



I

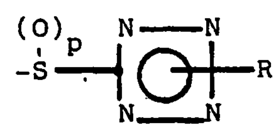
oder ein pharmazeutisch annehmbares Salz hiervon, worin

R_1 Wasserstoff, C_1—C_6-Alkyl oder C_3—C_8-Cycloalkyl ist,

R_2 Wasserstoff, C_1—C_6-Alkyl oder C_2—C_6-Alkenyl bedeutet,

R_3 Wasserstoff, C_1—C_{10}-Alkyl, Phenyl, durch C_1—C_{10}-Alkyl substituiertes Phenyl, Biphenyl oder Benzylphenyl ist,

R_4 für —$COOR_7$, —$CONR_8R_9$, —CONHOH, —SC(=NH)NH_2, Cyano, Thiocyanato,

 oder  steht,

wobei

R_7 Wasserstoff oder C_1—C_4-Alkyl ist,

R_8 und R_9 jeweils unabhängig Wasserstoff oder C_1—C_3-Alkyl sind oder zusammen mit dem Stickstoffatom einen Morpholinring oder einen N-Methylpiperazinring bilden, R Wasserstoff, C_1—C_4-Alkyl oder —CH_2—$COOR_7$ ist und p für 0, 1 oder 2 steht,

R_5 und R_6 jeweils unabhängig Wasserstoff oder C_1—C_3-Alkyl sind und

n für 0 bis 10 steht,

sofern (a) R_1 für CH_3 steht, R_2 für C_3H_7 steht, R_3 Wasserstoff ist, R_5 und R_6 jeweils Wasserstoff sind und R_4 für —$COOCH_3$ steht und n für 0 bis 2 oder für 4 bis 10 steht, und sofern (b) R_1 für CH_3 steht, R_2 für C_3H_7 steht, R_3 Wasserstoff ist, R_5 und R_6 jeweils Wasserstoff sind und R_4 für —$COOC_2H_5$ steht und n für 0 oder für 2 bis 10 steht.

2. Verbindung der Formel (I) gemäß Anspruch 1 oder ein pharmazeutisch annehmbares Salz hiervon, dadurch gekennzeichnet, daß R_1 für C_1—C_6-Alkyl steht, R_2 für C_1—C_6-Alkyl oder C_3—C_6-Alkenyl steht, R_3 Wasserstoff ist, R_5 Wasserstoff ist, R_6 Wasserstoff ist, R_4 für —COOH, 5-Tetrazolyl oder 5-Thiotetrazolyl steht und n für 1 bis 4 steht.

3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß R_1 Methyl ist und R_2 Propyl ist.

4. Verbindung nach Anspruch 1 oder 3, dadurch gekennzeichnet, daß n für 1 bis 4 steht.

5. Verbindung nach Anspruch 1, 3 oder 4, dadurch gekennzeichnet, daß R_4 für —COOH, 5-Tetrazolyl oder 5-Tetrazolylthio steht.